Docket No. LL401

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Inventor: LEVY, *et al.*

Serial No.: 08/962,740

Filing Date: November 3, 1997

For: IMMORTALIZED, HOMOZYGOUS STAT1-DEFICIENT MAMMALIAN CELL LINES AND THEIR USES

Art Unit: 1651

Examiner: L. Blaine Lankford

Commissioner of Patents
and Trademarks
Washington D.C. 20231

APPEAL BRIEF UNDER 37 CFR § 1.192

Sir:

In response to the Notification of Non-Compliance with 37 CFR § 1.192, mailed on May 22, 2001, the period for which expires on June 22, 2001 (one month from the mailing of the Notification), Applicants submit a complete amended Brief, in triplicate. The amended Brief now provides a concise explanation of the claimed invention, referring to the specification by page and line number. Applicants respectfully submit that the amended Brief is now in compliance with 37 CFR § 1.192.

(1) Party of Interest

The Party of Interest of the invention set forth in the present application is New York University, located at 70 Washington Square South, New York, NY, 10012.

(2) Corresponding Appeals or Interferences

There are no corresponding appeals or interferences.

(3) Status of Claims

The Notice of Appeal filed August 3, 2000 was taken with regard to claims 1-5 and 35-37. The claims appealed herein are claims 1-5, and 35-37.

(4) Status of Amendments

All amendments have been entered.

(5) Summary of Invention

The invention defined in the claims involved in this Appeal relates to an immortalized mammalian cell line homozygous for a *Stat1* null allele, as disclosed on page 3, lines 15-21 of the specification. In particular, the viral tropism of said cell line has been altered to be permissive for viral growth relative to that of the same cell line with wild type alleles of *Stat1*. (See page 6, line 34 to page 7, line 1). Preferably, the cells of said cell line are fibroblast cells capable of producing influenza virus at from about 10^3 to about 10^6 PFU/ml at about two days after having been infected. (See page 4, lines 1-6 and Table 2 on page 23). The present invention is based on the discovery that immortalized or transformed cells from *Stat1* knockout mice produce unexpectedly high titers of virus and exhibit altered viral tropism (See page 6, line 34 to page 7, line 1). The immortalized *Stat1* mammalian cell lines of the invention are useful for producing high titers of viral stocks, for producing recombinant viral vectors, for testing samples, especially clinical samples for the presence of virus, and for screening candidate compounds or drugs for anti-viral activity. (See page 7, line 1 to page 8, line 2).

(6) The issues presented in this Appeal are:

(1) Whether claims 1-5, and 35-37 would have been unpatentably obvious, within the meaning of 35 USC § 103, over Durbin *et al.*, (1996) Cell 84:443-450 (hereafter "Durbin")

in view of Jallat *et al.*, U.S. Patent No. 5,814,716 (hereafter "Jallat"), Leder *et al.*, U.S. Patent No. 5,087,571 (hereafter "Leder") and also in view of Todaro *et al.*, (1963) J.Cell. Biol. 17:299-313 (hereafter "Todaro"), at the time the invention was made.

(7) Grouping of Claims

For purposes of this Appeal, claims 1-5 and 37 should stand or fall together as a first group; claim 35 constitutes a second group; and claim 36 constitutes a third group, each of these groups being separately and independently patentable over Durbin in view of Jallat, Leder and Todaro. For the reasons set forth below, the claims should stand or fall according to the specific grouping of the claims.

(8) Arguments

Rejection of Claims 1-5, and 35-37 Under 35 U.S.C. § 103 Over Durbin in view of Jallat, Leder and Todaro

A. Claims 1-5 and 37 are Patentable Since There is No Motivation to Form An Immortalized *Stat1*-deficient Cell Line

Claims 1-5 and 37, directed to an immortalized mammalian cell line homozygous for a *Stat1* null allele, are not obvious over the disclosure of Durbin in view of Jallat, Leder and Todaro, since there is no motivation to combine these references to produce the claimed immortalized cell line.

Durbin teaches making transgenic mice completely deficient in the *Stat1* gene. As the Examiner acknowledges, Durbin does not teach developing an immortalized cell line from the mouse (Office Action mailed 7/9/99, at Page 2, Paragraph 2). The major focus of Durbin is the creation of *Stat1*-deficient mice in order to study the biological function of *Stat1 in vivo*. Specifically, Durbin discusses the creation of a *Stat1*-deficient mouse in order "to investigate further the generality of *Stat1* involvement in cytokine signaling and to probe the roles of *Stat1*- linked pathways under physiologic settings and during development" (Durbin at Page 443, last paragraph of the right column). In mentioning a previously described *Stat1* deficient cell line, Durbin states that, "the lack of responsiveness of the parental cell line to other cytokines, and the uncharacterized nature of the *Stat1* defect have made generalizations concerning *Stat1* function difficult to draw." (Durbin at Page 443, last paragraph of the right column). Durbin made *Stat1* knockout mice in order to study how *Stat1*- deficient cells

responded to leukemia inhibitory factor (LIF) and interferon (IFN) (Durbin at Page 444-445). Moreover, Durbin cultured *Stat1* mutant embryonic fibroblasts in order to study the induction of IFN gene transcription in response to viral infection (Durbin at Page 444).

However, Durbin does not disclose or suggest making an immortalized *Stat1* deficient cell line. Further, Durbin does not suggest the need for, or the benefits of, such an immortalized *Stat1*-deficient cell line. In fact, the authors were able to achieve their results without immortalizing the *Stat1*-deficient cell line that they cultured. Durbin never discloses or suggests any reason to prepare an immortalized *Stat1*-deficient cell line. Thus, Durbin clearly does not suggest an immortalized *Stat1*-deficient cell line or the utility of such immortalized cell line as hosts for producing viral stocks, for producing recombinant viral vectors, or for detecting viruses and the like. One skilled in the art would therefore not be motivated by Durbin to spend the time, money and effort making such an immortalized cell line.

The secondary references, Leder, Jallat and Todaro, do not remedy the deficiencies of Durbin as none of these references relate to *Stat1*-deficient transgenic animals or cell lines. Leder discloses the creation of a transgenic mouse containing an activated oncogene and a method for providing a cell culture from a transgenic animal in order to develop a genetically-sensitized model for assaying various compounds' carcinogenic properties *in vivo*. Jallat creates a transgenic liver tumor cell line containing an exogenous DNA sequence for human factor IX and a second exogenous DNA sequence encoding either the SV40 virus T-antigen or the mouse c-myc gene, in order to produce biologically active factor IX which can be used to treat patients with type B hemophilia. (Jallat at Column 1, Lines 10-65; Column 3, Lines 22-27 and Lines 40-42; Column 4, Lines 15-19). Todaro discloses that spontaneously immortalized cell lines may be derived from normal Swiss mouse embryo cells (and possibly other cell types) after successive cell culture transfer and teaches that such an "established cell may have a bearing on the problem of carcinogenesis". (Todaro, page 299, lines 14-15). None of these references disclose or suggest creating an immortalized *Stat1*-deficient cell line. As such, they do not cure the deficiencies of Durbin.

"Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *In re Geiger,* 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed Cir. 1987). Merely because it may have been known to make immortalized cell lines from transgenic mice, does not provide any motivation at all to make an immortalized cell line from a *Stat1*-

deficient mouse. There is no teaching or suggestion why such a cell line might be useful. The cell lines disclosed in Leder, Jallat and Todaro do not have any relationship whatsoever to a *Stat1*-deficient cell line. As such, these references absolutely do not provide any motivation to make the claimed immortalized *Stat1*-deficient cell line from Durbin's *Stat1*-deficient transgenic mouse. The mere existence of *Stat1*-deficient mice cannot be a suggestion to make immortalized *Stat1*-deficient cell lines. The Examiner must show that the references render the claimed invention *prima facie* obvious, not simply a general method of making immortalized cells.

Absent impermissible hindsight gleaned from the subject application, one of ordinary skill in the art would not have been motivated to combine Durbin with Jallat, Leder, or Todaro. The Examiner's alleged motivation to combine these references is "because the immortalization of cells and the desirabilities of immortalization using such tools as SV40 is notoriously old and well known in the art." Applicants respectfully submit that this reasoning is not a motivation to modify Durbin to form an immortalized *Stat1*-deficient cell line. Merely because it may have been generally known to immortalize cells does not provide any motivation to immortalize the specific cells from the transgenic mouse disclosed in Durbin, which are completely unrelated to and have a different utility from those cell lines disclosed in Leder and Jallat. *See, e.g., In re Laskowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989)("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."). To establish a *prima facie* case of obviousness there must first be some suggestion or motivation, either in the references itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. See *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Int. 1985). See also *Ex parte Skinner*, 2 USPQ2d 1788 (Bd. Pat. App. & Int. 1986). The question here is not whether the cell line of the *Stat1*-deficient mouse disclosed in Durbin could be immortalized, but whether one would have been motivated to perform such immortalization of Durbin's *Stat1*-deficient cell line based on Jallat, Leder, and Todaro, as suggested by the Examiner. Applicants submit that one of ordinary skill in the art would not have been motivated to perform such immortalization of Durbin's *Stat1*-deficient cell line.

Accordingly, the rejection of claims 1-5 and 37 under 35 U.S.C. § 103 (a) over Durbin in view of Jallat, Leder and Todaro should be reversed.

B. Claim 35 Is Separately Patentable

Claim 35 is directed to an immortalized mammalian cell line homozygous for a *Stat1* null allele, wherein viral tropism of said cell line has been altered to be permissive for viral growth relative to that of the same cell line with wild type alleles of *Stat1*. This claim is separately patentable over Durbin in view of Jallat, Leder and Todaro, as these references fail to suggest that viral tropism of such an immortalized cell line is permissive for viral growth relative to that of the same cell line with wild type alleles of *Stat1*.

There is nothing in Durbin, Jallat, Leder or Todaro which suggests this feature of the claimed invention. Further, none of the Official Actions have explained why it would have been allegedly obvious that an immortalized *Stat1*-deficient cell line is permissive for viral growth relative to that of the same cell line with wild type alleles of *Stat1*. There is no reason of record why this claim has been rejected. As such, the rejection of claim 35 should not be sustained.

C. Claim 36 Is Separately Patentable

Claim 36 is directed to an immortalized mammalian cell line homozygous for a *Stat1* null allele, wherein the cells of said cell line are fibroblast cells capable of producing influenza virus at from about 10^3 to about 10^6 PFU/ml at about two days after having been infected. This claim is separately patentable over Durbin in view of Jallat, Leder and Todaro, as these references fail to suggest that fibroblast cells from the claimed immortalized cell line are capable of producing influenza virus at from about 10^3 to about 10^6 PFU/ml at about two days after having been infected.

There is nothing in Durbin, Jallat, Leder or Todaro which suggests this feature of the claimed invention. Further, none of the Official Actions have explained why it would have been allegedly obvious that fibroblast cells from an immortalized mammalian cell line homozygous for a *Stat1* null allele are capable of producing influenza virus at from about 10^3 to about 10^6 PFU/ml at about two days after having been infected. In fact, there is no reason of record why this claim has been rejected. As such, the rejection of claim 36 should not be sustained.

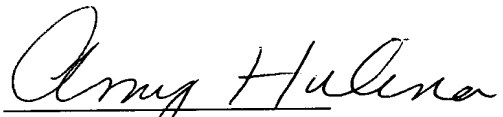
For at least the foregoing reasons, the Honorable Board of Patent Appeals and Interferences should find that the Examiner erred in finally rejecting claims 1-5, and 35-37

under 35 U.S.C. § 103 over Durbin in view of Jallat, Leder and Todaro. Accordingly, it is respectfully requested that this rejection be reversed.

The Applicant believes no additional fee is due, but authorizes charging of any underpayment or crediting of any overcharge to Deposit Account No. 11-0600.

Respectfully submitted,

June 21, 2001

By 
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APPENDIX OF CLAIMS ON APPEAL

1. An immortalized mammalian cell line homozygous for a *Stat1* null allele.

2. The cell line of Claim 1, wherein mammalian is murine or human.

3. The cell line of Claim 1, wherein said cell line was obtained by selection for spontaneously immortalized cells or by transformation.

4. The cell line of Claim 1, wherein the cells of said cell line are endothelial cells, epithelial cells, hematopoetic cells, bone marrow cells, kidney cells or liver cells.

5. The cell line of Claim 4, wherein said epithelial cells are fibroblast cells.

35. The immortalized mammalian cell line of Claim 1, wherein viral tropism of said cell line has been altered to be permissive for viral growth relative to that of the same cell line with wild type alleles of *Stat1*.

36. The immortalized mammalian cell line of Claim 35, wherein the cells of said cell line are fibroblast cells capable of producing influenza virus at from about 10^3 to about 10^6 PFU/ml at about two days after having been infected.

37. The immortalized mammalian cell line of Claim 1, wherein said cell line is the cell line designated as ATCC accession number CRL-12425.